Botulinum Toxin – a promising new treatment for overactive bladder

C. Persu¹, D. Castro-Diaz², S.C. Gutui³, J. Lavelle³, P. Geavlete¹

¹ Spitalul Clinic Sf Ioan, Bucuresti
² University Hospital of Canary Islands, Tenerife, Spain
³ VAPAHCs, Palo Alto, CA, USA

Introduction

Overactive bladder (OAB) is a symptom syndrome characterized by urgency-frequency with or without urgency incontinence that may affect the patient quality of life [1].

The International Continence Society (ICS) defines it as “urgency, with or without urge incontinence, usually with frequency and nocturia if there is no proven infection or other etiology.” More specifically, the ICS refers to this constellation of symptoms as the “overactive bladder syndrome”. This symptom combination may be suggestive for detrusor overactivity, but can also be due to other forms of lower urinary tract dysfunction, and sometimes urodynamics is indicated. These terms can be used if there is no proven infection or other obvious pathology. Ure syndrome or urgency–frequency syndrome are described as synonyms of OAB [2].

Current treatments are sometimes unsuccessful in completely eradicating the urgency sensation. Behavioral therapy or pelvic floor muscle training have been used to relieve this bothersome syndrome [3]. Some patients with OAB and hypersensitive bladder may respond to antimuscarinic agents [4] but this treatment has some adverse effects such as dizziness, dry mouth, blurred vision, constipation, which may be intolerable to some patients [5]. Acetylcholine, derived from non-neuronal as well as neuronal sources and during bladder filling, directly or indirectly stimulates afferent activity from the bladder, contributing to OAB and DO. By inhibiting this effect, antimuscarinics may decrease OAB symptoms and DO without affecting the voiding contraction.

Intra-detrusor botulinum A toxin (BTX-A) injection has been tried and satisfactory results have been achieved in increasing bladder capacity and decreasing the urgency sensation in patients with neurogenic or idiopathic detrusor overactivity [6]. However, increased postvoid residual volume (PVR) or urinary retention which may develop soon in the first post–treatment month may prohibit its wide spread application in patients with mild to moderate symptoms refractory to muscarinic agents [7].

The aim of this paper is to review the up-to-date information regarding the use of botulinum toxin treatment and to summarize the current off-label usage of this agent to treat OAB, including clinical results, injection techniques, and adverse events.

Corespondenţă: Prof. Dr. Petrişor Geavlete
Clinica de Urologie, Spitalul Clinic de Urologie „Sf. Ioan”, Șos. Vitan Bârzești, București, 022358
Tel/Fax: 021 334 5000
Email: geavlete@gmail.com
The urothelium - where the “negotiations” take place

The urothelium, which has been traditionally viewed as a passive barrier, is also proved to have specialized sensory and signaling properties that allow it to respond to chemical and mechanical stimuli and to engage in reciprocal chemical communication with neighboring nerves in the bladder wall. These properties include:

1. expression of nicotinic, muscarinic, tachykinin, adrenergic, and capsaicin (TRPV1) receptors;
2. responsiveness to transmitters released from sensory nerves;
3. close physical association with afferent nerves;
4. the ability to release chemical mediators such as ATP and nitric oxide that can regulate the activity of adjacent nerves and thereby trigger local vascular changes and/or reflex bladder contractions. [7-1]

The role of ATP in urothelial-afferent communication has attracted considerable attention because bladder distention releases ATP from the urothelium [8] and intravesical administration of ATP induces bladder hyperactivity, an effect blocked by administration of P2X purinergic receptor antagonists that suppress the excitatory action of ATP on bladder afferent neurons. Mice in which the P2X3 receptor was knocked out exhibited hypoactive bladder activity and inefficient voiding, suggesting that activation of P2X3 receptors on bladder afferent nerves by ATP released from the urothelium is essential for normal bladder function. In humans and cats with interstitial cystitis, a painful bladder condition, ATP release from urothelial cells is enhanced. Transmitter release mechanisms in the urothelium may also be a target for botulinum toxin A (BTX-A), which is injected into the bladder wall to treat patients with various types of detrusor overactivity. BTX-A can act at multiple sites in the bladder, because it reduces the release of ATP into the bladder and suppresses the release of acetylcholine and norepinephrine from autonomic nerves [9]. BTX-A also blocks the stretch-evoked release of ATP from cultured urothelial cells. Thus, the clinical efficacy of BTX-A in the treatment of bladder dysfunction may be related to its action on urothelial sensory mechanisms as well as to its effects on neurotransmitter release from efferent nerves.

It seems that a nexus of suburothelial myofibroblasts may respond to ATP in a mode similar to the activation of ATP-gated P2Y receptors [10,11]. The urothelial release of ACh and ATP on bladder filling has been found to increase with ageing [12] and in spinal cord neurogenic detrusor overactivity (NDO), implicating an abnormal release of these neurotransmitters in the pathophysiology of DO. In the treatment of idiopathic detrusor overactivity with intradetrusor injections of BTX-A, a decreased immunoreactivity of P2X3 expression in suburothelial fibers has been noted, which correlates with improvement in the sensation of urgency [13].

The actual pathophysiology of OAB has not been fully understood. Recently, the urothelium and suburothelial space have received renewed interest because of their possible role not only in mediating solute transport but also in sensing bladder fullness [14] The stretch-sensing lamina propria may transmit sensory signals as well as mediate the detrusor reflex [15]. A change in hydrostatic pressure on the apical face of the urothelium results in ATP generation, which is postulated to activate P2X3 receptors on sensory nerves. The P2X3 receptors are colocalized with vanilloid receptor-1 and are believed to be involved in afferent pathways that control urinary bladder volume reflexes [16]. Recent work indicates that the nerve growth factor (NGF) is involved in the ongoing regulation of neural function, as well as in inflammation and pain [17]. Clinical and experimental data also link increased levels of NGF in the bladder tissue and urine to painful inflammatory conditions in the lower urinary tract, such as interstitial cystitis and chronic prostatitis. Recent investigations have shown that intravesical BoNT-A reduces levels of NGF in the bladder in IDO as well as NDO [18].
It is also possible that the chronic symptomatology in bladder hypersensitivity is due to central sensitization and persisting abnormality or activation of the afferent sensory system [19]. Intradetrusor injection of BTX-A has been found to modulate the release of neurotransmitters from sensory nerve endings, and effectively modulate the inflammatory process mediated by nociceptive afferent nerve dysfunction [20].

**Botulinum toxin – old substance, new indications**

Botulinum toxin (BTX), first isolated by van Ermengem in 1895, is the most potent biological agent known to man. BTX's mechanism of action has been traditionally described as inhibiting acetylcholine release at the presynaptic cholinergic junction. However, in later sections we will present evidence that BTX could inhibit other transmitter systems and cellular processes also thought to play an important role in the development of bladder overactivity. Clinically, the urologic community's initial experience with botulinum toxin A (BTX-A) was to treat bladder overactivity resulting from neurologic trauma (i.e. spinal cord injury, etc.). Over the past few years, however, the use of BTX-A has been expanded to treat patients with non-neurogenic overactive bladder (OAB). The rapid expansion of BTX to treat OAB is basically due to the inadequacy of current standard pharmacologic treatment (i.e. antimuscarinic agents) as well as to the demonstration of BTX's efficacy, durability, and tolerability in early clinical series. However, nowadays the use of BTX in the bladder is not authorized by the Food and Drug Administration (FDA) and it is considered an off-label indication, so caution should prevail exuberance.

What do we know so far?

A Medline search from 1966 to 2006 using the word “bladder” combined with the words “botulinum toxin” will give a total of 176 records and cross-references, demonstrating an exponential growth in the number of articles using these keywords as well as the number of patients treated with bladder BTX injection. In recent years, the ongoing clinical trials with BTX offer a more systematic approach to the problem. We used only full manuscripts in this review from 2000 to the present, limiting the extent of our search to the year in which BTX was first described to treat OAB symptoms. Information was collected regarding indications for usage, study design, type of botulinum toxin, site of injection, dosage, efficacy, and adverse effects (local and systemic).

BTX-A is a durable, yet reversible, treatment option as nerves eventually recover their original function. However, although the clinical effects of BTX-A in skeletal muscle spasticity typically last three to four months, longer durations have been observed following BTX-A injection into the bladder's smooth muscle (six months or more). Similar clinical responses from BTX-A treatment in other autonomic disorders (e.g. axillary/palmar hyperhidrosis, gustatory sweating, sialorrhea) have been described (range 4–36 months), suggesting that differences in toxin effect or reinnervation may account for the more prolonged clinical responses observed in autonomic versus somatically innervated tissues [21,22]. Recent studies have identified the binding site for the BTX-A heavy chain C-terminus to be a synaptic vesicle protein called SV2 [23]. Because SV2 is a synaptic vesicle protein, its exposure on the surface of nerve terminals increases when more neurotransmitter is released. In this regard, BTX-A preferentially targets nerves that are more active.

Seven immunologically distinct neurotoxins are known: types A, B, C, D, E, F, and G. Only botulinum toxin types A and B are commercially available worldwide. Currently, two types of botulinum toxin are available in the United States: **type A** (Botox®; Allergan, Irvine, CA) and **type B** (Myobloc®; Elan Pharmaceuticals, Inc., San Francisco, CA). Two other formulations of botulinum toxin A are available in Europe (Dysport®; Ipsen Ltd, Slough, United Kingdom; and Xeomin®; Merz Pharma GmbH, Frankfurt am Main, Germany).

The potency of each toxin is expressed in units of activity. Botox® is supplied as a vacuum dried powder and should be stored at or below -5°C. The vial contains 100 international units (IU) that are diluted with preservative-free normal saline to the desired final concentration. Manufacturer’s instructions state that care must be taken to avoid agitation of the toxin while mixing to avoid foaming and possible loss of potency (Botox® product insert, Allergan, Inc., Irvine, CA). In addition, one is instructed to utilize the toxin within 4 hours of mixing, and one should never
refreeze but should refrigerate unused portions of toxin. However, recent clinical studies have brought into question these recommendations. A recent multicenter, double blind study demonstrated no deterioration in clinical efficacy of Botox® when applied up to 6 weeks after reconstitution with saline [24]. However, until larger or more sensitive studies more clearly identify the loss of toxicity with reconstitution, it is recommended that the solution is mixed with as little agitation and foaming as possible. Proper mixing includes limiting the rapid descent of the syringe plunger to the vacuum pull of the diluent and, once diluted, gently rotating and swirling the vial [25]. In contrast to BTX-A preparations, Myobloc® is already premixed in liquid form, and therefore does not have to be reconstituted with saline. Botox® dosage is expressed in terms of international units, 1 IU representing the lethal dose (LD50) to kill 50% of a colony of 10–20 Swiss Webster mice by intraperitoneal injection. However, preparations of BTX from different companies or different batches within a company may have variable potencies even if the same number of units is used, because lethal potency depends not only on the amount of toxin but also other biological factors that do not always correlate to therapeutic potency [25-1].

For example, Botox® is comprised of 900-kDa neurotoxin complexes, whereas Dysport® is a mixture of 500–900-kDa neurotoxin complexes. Clinical observations suggest that Botox® is associated with a lower rate of adverse events than is Dysport®[19–21], data which is consistent with preclinical evidence suggesting that the larger, more uniform size of the Botox® neurotoxin complex protein (i.e. 900 kDa) minimizes unwanted migration and the development of adverse events. [26] 22 Thus, while Botox® has been reported to be three times as potent therapeutically as an equal amount of Dysport® and 50–100 times as potent as Myobloc (in LD50 units), differences in systemic effects versus muscle weakening ratios between these agents make it difficult to use a strict dose ratio when comparing these preparations.

Clinical Data

In neurogenic detrusor overactivity, the use of BTX-A in the urinary bladder was first described in a manuscript form by Schurch and colleagues who demonstrated a significant increase in mean maximum bladder capacity (296 to 480 ml, \( p = 0.016 \)) and a significant decrease in mean maximum detrusor voiding pressure (65 to 35 cmH2O, \( p = 0.016 \)) in 21 patients with detrusor hyperreflexia (DH) who were injected with BTX-A. [27] Seventeen of 19 patients were completely continent after six weeks follow-up, and were very satisfied with the procedure. Interestingly, baseline improvement in urodynamic parameters and incontinence persisted at 36 weeks in their followup of 11 patients.

In the largest clinical series available to date, a multicentric retrospective study which examined 200 patients with neurogenic bladder treated with intravesical BTX-A injections, both the three and six month follow-up demonstrated that mean cystometric bladder capacity increased while mean voiding pressure decreased significantly [28]. A strong impetus driving clinical trials examining the effects of BTX-A on detrusor overactivity was provided by the only randomized, placebo controlled trial investigating the effects of two doses of Botox® (i.e. 200 or 300 units) versus saline injection on various parameters including urodynamic measurements, urinary incontinence episodes, and quality of life questionnaires. Significant decreases in incontinence episodes (approximately 50%), significant increases in maximal cystometric capacity (approximately 170–215 ml), and significant improvements in quality of life scores were demonstrated in both BTX-A treatment groups compared to controls. Beneficial effects lasted the duration of the study (6 weeks). The study was not powered to detect statistical differences between the two BTX-A doses injected, but no safety concerns were raised.

Ruffion and colleagues utilized the Dysport® preparation of BTX-A to compare the effect of 500 U or 1000 U in 45 patients with neurogenic detrusor overactivity. [29] While maximal bladder capacity and median duration of response (4.83 vs. 10.45 months, respectively) were increased with the higher Dysport® dose, one patient complained of generalized muscle weakness for 1 month following injection that prevented her from performing her normal transfer functions. The authors postulated that 750 U would be the most suitable dose to maximize efficacy while minimizing adverse events.

Popat and colleagues prospectively examined the effects of BTX-A detrusor injection in 44 patients with neurogenic and 31 patients with nonneurogenic detrusor overactivity proven by preoperative urodynamic studies [30]. The benefits of treatment in both patient populations included significant increases in maximal cystometric capacity and significant reductions
in incontinence episodes and urinary urgency. Impressively, 60.3% of all patients achieved complete continence.

Their results are supported by smaller comparative studies demonstrating the efficacy of BTX-A in neurogenic and non-neurogenic populations. [31] What is most meaningful from all of these studies of BTX-A treatment of bladder overactivity is that many patients successfully treated were either poorly responsive or refractory to antimuscarinic therapy. This finding supports basic research described earlier that BTX-A works through other mechanisms in addition to the inhibition of ACh release from parasympathetic nerve terminals. Ghei and colleagues investigated the effectiveness of BTX-B in 20 patients with either neurogenic or non-neurogenic detrusor overactivity. [32] The study was a randomized, double-blind crossover trial, and demonstrated significant reductions in urinary frequency and episodes of incontinence between active treatment and placebo. However, the low durability of BTX-B’s effects was evidenced by the minimal carry-over effect noted upon crossing over after a short-time period (i.e. 6 weeks).

Rapp and colleagues initially presented a series of 35 patients with refractory overactive bladder symptoms treated with 300 units of BTX-A detrusor injections. Patient response to treatment was assessed using the Incontinence Impact Questionnaire (IIQ-7) and Urogenital Distress Inventory (UDI-6) questionnaire. [33] At the 3-week follow-up, mean IIQ and UDI symptom scores decreased significantly by 28% and 24%, respectively. Symptom improvement persisted in 14 patients followed up to 6 months after treatment, and pad usage per day decreased from a mean of 3.9 to 1.8. Beneficial effects of BTX-A injection were also demonstrated in several smaller series, including one series of patients who presented with overactive bladder symptoms but in whom urodynamic examination excluded detrusor overactivity.

Schmid and colleagues recently presented a prospective, non-randomized study of 100 patients with idiopathic overactive bladder resistant to antimuscarinic treatment. [34] Patients were injected with 100 units of BTX-A at 30 sites within the detrusor muscle. Urgency resolved completely in 72% and incontinence disappeared in 74% of patients, 4 weeks following injections. Mean maximal bladder capacity increased by 56%, and the beneficial effects of BTX-A lasted approximately 6 months. Poor response was noted in 8% of patients treated, and was thought to result from decreased bladder compliance secondary to bladder wall fibrosis.

As for pediatric patients, investigators have also successfully utilized intravesical BTX-A to treat neurogenic bladders in pediatric myelomeningocele patients. Within this patient population, BTX-A treatment could function as an alternative to bladder augmentation in the 8–12% of patients who fail conservative treatment (e.g. clean intermittent catheterization (CIC) and anticholinergic medications). Schulte-Baukloh and colleagues presented data on 17 myelomeningocele children (mean age 10.8 years) with detrusor hyperreflexia and intravesical pressures exceeding 40 cmH2O, who were either resistant to high-dose anticholinergic medication or who developed unacceptable anticholinergic side effects. Patients were injected with 85–300 units of Botox® in 30–40 sites of the bladder. Urodynamic follow-up was performed 2–4 weeks after injection.

BTX-A treatment induced significant increases in maximal bladder capacity (56.5%) and compliance (121.6%), and a significant decrease in maximal detrusor pressure (32.6%). [35] Botulinum toxin A proved effective in spinal cord injured patients with poor detrusor compliance. While BTX-A has been shown to reduce detrusor overactivity in patients with neurogenic bladders, earlier studies did not investigate whether BTX-A treatment could improve bladder compliance, and, possibly, reduce the need for invasive surgery. Klapahjone and colleagues examined the effects of injecting 300 units of Botox® into the detrusor muscle of 10 spinal cord injured patients with low bladder compliance. [36]

Significant improvements were noted in mean bladder compliance (6.5_5.0 to 13.2_5.2 ml/cmH2O) and mean functional bladder capacity (mean increase of 156 ml). In addition, 70% of patients were completely continent after six weeks follow-up, and continence was maintained in 50% of patients for nine months after the injection. These results are in stark contrast to the poor results achieved in eight patients with idiopathic bladder overactivity and decreased detrusor compliance. However, beneficial effects of BTX-A in patients with poor detrusor compliance should only be expected if the decreased compliance is a result of increased neurogenic tone of the detrusor muscle and not secondary to bladder wall fibrosis.

Grosse and colleagues evaluated the effectiveness of repeated detrusor injections of BTX-A. [37] A total of 49 patients with refractory neurogenic detrusor over-
activity received between two to five injections of BTX-A. The authors found significant and similar reductions in detrusor overactivity and in the use of anticholinergic medication, in addition to significant increases in bladder capacity and compliance after both the first and second injections with BTX-A. The average interval between injections was 11 months. As more patients are repeatedly treated with BTX-A injections into the lower urinary tract, urologists will gain better insight into patients’ risk of developing antibodies and becoming clinically non-responsive. Similar to studies in adults, investigators have also found that children respond favorably to repeated injections with BTX-A.

More important, not only does BTX-A appear to have little effect on neuronal architecture within the bladder, but investigators have also shown that BTX-A does not induce bladder inflammation, edema, or fibrosis. [39] These findings should alleviate concerns from urologists that repeated detrusor injections with BTX-A will induce bladder wall fibrosis and lead patients more rapidly to surgical options.

Where and how much to inject?

For adult patients, doses of Botox® range from 200 to 300 units with a Dysport® dose equivalence of approximately 3 Dysport® : 1 Botox® unit. However, no controlled studies have been performed to determine the optimum dose or toxin dilution in neurogenic and OAB patient populations. Current data suggest there is no difference in efficacy between usual doses, but a higher dose may associate a higher adverse reactin rate. In children, Schulte-Baukloh et al. utilized 12 units/kg of Botox®, similar to doses given in other neuropediatric populations [40].

The injection technique requires a cystoscopic evaluation of the bladder. Then, using a bladder injection needle with a rigid cystoscope, or, alternatively, using a 27-gauge disposable injection needle and a non-disposable injection needle sheath (Olympus, Inc.) with a flexible cystoscope, BTX-A is injected into 10–40 sites within the detrusor muscle targeting the trigone, base of the bladder, and lateral walls, while avoiding the dome and posterior walls to prevent inadvertent perforation and bowel injection. The 10-site injection technique is utilized for patients with idiopathic overactive bladders and is a modification of the 30–40-site injection technique previously described [41]. Some authors suggest that the trigone should be avoided due to the increased risk of urethral reflux, while others indicate trigone injections only in patients with a painful bladder syndrome, because of the rich sensory innervation in this area. That aspect may also play a role in the symptoms of bladder overactivity and could be impacted by BTX treatment. Nevertheless, no data is available to date that argues the possibility of vesicoureteral reflux (e.g. pyelonephritis).

As BTX-A is becoming more widespread within the urologic community and non-neurogenic populations are offered this treatment, future studies need to identify the minimal effective dose required to achieve efficacy while diminishing local side effects. Issues to be further investigated include total toxin dosage, toxin dilution volume, and number and location of injection sites. In most hands, 10 injections of a total of 100 units of BTX-A into the bladder trigone and base may effectively suppress irritative symptoms in patients with refractory OAB without inducing elevations in PVR. [41-1]

Cost-to-benefit Ratio

Some early open-label studies have shown that efficacy persists with repeated injections of BTX-A; however, large, long-term, observational studies are needed to confirm both efficacy and safety.

The current evidence suggests that repeated injections are at least as effective as the first injection, provide persistent improvement, and do not lead to exa-
ceration of symptoms, drug tolerance, changes to bladder compliance, or detrusor fibrosis [42]. Encouraging initial data from a completed multinational, dose-finding, phase 2 study of BTX-A in idiopathic OAB were recently presented at the American Urological Association Annual Meeting in Chicago, Illinois [43]. In addition, several multinational, phase 3 studies of BoNT-A in patients with neurogenic OAB are currently ongoing (ClinicalTrials.gov, 2009).

In patients with NDO who have opted to receive BTX-A injections as opposed to more invasive surgical procedures, such as bladder augmentation or sacral neuromodulation, significant cost savings can be expected. One cost analysis found that the three-year cumulative cost of bladder augmentation for OAB exceeded $14,000, and sacral neuromodulation cost over $25,000, whereas the cumulative cost for BTX-A injections over three years was $7,651 (all cost estimates in 2007 U.S. dollars) [43]. The lack of a prolonged hospital stay and minimal pre-operative testing required for BTXA injections allow for improved quality of life because little interruption to daily routine has occurred.

One final remark is that previous injection of botulinum toxin does not contraindicate other future treatments, such as neuromodulation or bladder augmentation, so this treatment should be tried before going on to a more invasive one.

References

23. Dong M, Yeh F, Tepp WH et al. SV2 is the protein receptor for botulinum neurotoxin A. Science 2006; 312: 592–6.


41-1 Dmochowski R, Efficacy and safety of onanobotulinum toxin for idiopathic overactive bladder a double-blind placebo controlled, randomized dose ranging trial, J. Urol 2010 Dec; 184(6): 2423-8
